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CLINICAL RESEARCH

Impact of multivessel disease on myocardial perfusion and survival among patients undergoing primary percutaneous coronary intervention with glycoprotein IIb/IIIa inhibitors

Impact de lésions coronaires multitronculaires sur la perfusion myocardique et sur la survie chez des patients d'une revascularisation coronaire percutanée sous anti GPIIbIIIa

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Abbreviations: CAD, coronary artery disease; IRA, infarct-related artery; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

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Summary

Background. — Although primary angioplasty achieves thrombolysis in myocardial infarction (TIMI) 3 flow in most patients with ST-elevation myocardial infarction, epicardial recanalization does not guarantee optimal perfusion in a large proportion of patients. The influence of multivessel disease on myocardial reperfusion and survival after primary angioplasty has not been extensively investigated.

Aim. — To evaluate the impact of multivessel disease on myocardial perfusion and survival in a large cohort of patients with ST-elevation myocardial infarction treated with angioplasty and glycoprotein (GP) IIb/IIIa inhibitors.

Methods. — This analysis is based on 1494 patients undergoing primary angioplasty included in the EGYPT database. Myocardial perfusion was evaluated by angiography or ST-segment resolution, whereas infarct size was estimated by using peak creatine kinase-MB (CK-MB). Follow-up data were collected between 30 days and 1 year after primary angioplasty.

Results. — Multivessel disease was observed in 870 patients (58.2%). The extent of coronary artery disease was associated with age, diabetes, hypertension, previous myocardial infarction, previous revascularization, abciximab treatment and longer ischaemic time, and was independently associated with impaired angiographic myocardial perfusion (adjusted odds ratio 1.18, 95% confidence interval [CI] 1.01–1.40, $P=0.049$). At 208 ± 160 days, the extent of coronary artery disease was independently associated with higher mortality (adjusted hazard ratio 1.54, 95% CI 1.06–2.24, $P=0.022$).

Conclusions. — Among patients with ST-elevation myocardial infarction undergoing primary angioplasty with GP IIb/IIIa inhibitor treatment, the extent of coronary artery disease was independently associated with impaired myocardial perfusion and survival.

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MOTS CLÉS

Angioplastie
primaire ;
Lésions
pluritrunculaires ;
Perfusion
myocardique ;
Mortalité

Résumé

Justification. — Bien que l'angioplastie primaire aboutisse à un flux TIMI 3 chez la majorité des patients ayant un infarctus du myocarde avec sus-décalage du segment ST (STEMI), la recanalisation épicardique ne garantit pas une reperfusion optimale dans une proportion significative de patients. L'influence de la présence de lésions coronaires pluritrunculaires sur la reperfusion myocardique ainsi que la survie au décours d'une angioplastie primaire n'a pas été évaluée de façon détaillée.

Objectifs. — Évaluer l'impact de lésions coronaires pluritrunculaires sur la perfusion myocardique et la survie au sein d'une cohorte de patients ayant un STEMI traité par angioplastie primaire et sous anti-GPIIb-IIIa.

Méthode. — Cette analyse a inclus 1494 patients bénéficiant d'une angioplastie primaire, inclus dans la base EGYPT. La perfusion myocardique a été évaluée angiographiquement ou sur la résolution du sus-décalage du segment ST et la taille de l'infarctus a été évaluée sur le pic de CPK-MB. Les données de suivi ont été collectées à j30 et à un an après l'angioplastie primaire.

Résultats. — Les lésions coronaires pluritrunculaires ont été observées chez 870 patients (58,2%). L'étendue de la maladie coronaire était associée à l'âge, au diabète, à l'hypertension artérielle, à un antécédent d'infarctus du myocarde, à un antécédent de revascularisation coronaire, à un traitement par abciximab, et à une durée prolongée de l'ischémie et était associée de façon indépendante à une altération de la perfusion myocardique évaluée en angiographie (*odds ratio* ajusté 1,18, IC 95 % 1,01–1,4, $p=0,049$). À $j208 \pm 160$, l'étendue de la maladie coronaire est associée de façon indépendante à une surmortalité (*hazard ratio* ajusté 1,54, IC 95 % 1,06–2,24, $p=0,022$).

Conclusion. — Parmi les patients ayant un STEMI traité par angioplastie primaire, sous anti-GP IIb/IIIa, l'étendue de la maladie coronaire est attestée de façon indépendante à une altération de la perfusion myocardique et à la survie.

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Background

In patients presenting with acute myocardial infarction primary angioplasty improves survival compared with thrombolysis, due mainly to a large percentage of restoration of TIMI 3 flow [1,2], with further improvement in clinical outcomes observed with the use of new antithrombotic therapies and devices [3–10]. However, epicardial recanalization does not guarantee optimal myocardial perfusion, which remains suboptimal in a relatively large proportion of patients [11,12]. In addition, concomitant atherosclerosis in coronary vessels other than the infarct-related artery (IRA) is observed in a notable proportion of patients undergoing primary percutaneous coronary intervention (PCI), ranging from 40% to 50% [13–17]. The prognostic impact of multivessel coronary artery disease (CAD) has not been extensively investigated [18–20]. Thus, the aim of the current study was to investigate the impact of multivessel disease on procedural success, myocardial reperfusion, infarct size and mortality in patients with ST-elevation myocardial infarction (STEMI) enrolled in Early Glycoprotein IIb/IIIa Inhibitors in Primary Angioplasty (EGYPT) database.

Methods

Our initial population comprises patients with STEMI treated by primary angioplasty and included in the EGYPT database. Detailed data on the EGYPT cooperation have been published [8]; characteristics of the studies included are reported in Table 1. All patients were admitted within 12 h of symptom onset, received aspirin (500 mg intravenously) and heparin (10,000 IU intravenously) as well as glycoprotein (GP) IIb/IIIa inhibitors before the procedure (in the cardiac care unit or ambulance [early] or in the cath lab [late]), and were on double oral antiplatelet therapy (aspirin and clopidogrel) for 4 weeks or more, after stent implantation. Thereafter, aspirin (or clopidogrel, in patients with side-effects from aspirin) was continued as monotherapy.

Data from angiograms and electrocardiograms were provided by each principal investigator (not analysed by a central core laboratory). Analysis of angiograms was based on standard definitions [8]. Angiographic myocardial perfusion was evaluated by myocardial blush grade [21] or myocardial perfusion grade [22]. Optimal myocardial reperfusion was considered as myocardial blush grade 3 or myocardial perfusion grade 3. Distal embolization was defined as an abrupt 'cut-off' in the main vessel or one of the coronary branches of the infarct-related artery (IRA), distal to the angioplasty site [8]. Even though ST-segment analysis was performed according to the prespecified criteria of each trial, data were provided according to uniform thresholds (< 30% no resolution; 30–70% partial resolution; > 70%

complete resolution). Infarct size was estimated using peak creatine kinase (CK) and CK-MB.

Clinical outcome was assessed between 30 days and 1 year after primary angioplasty by telephone interview or at medical visit. The primary study outcome was mortality at follow-up; the secondary study outcome was myocardial perfusion as evaluated by myocardial blush grade and ST-segment resolution.

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 statistical package. Continuous data are expressed as mean \pm standard deviation (SD) and categorical data as percentage. The ANOVA test was used for continuous variables, and the Chi² test or Fisher's exact test was used for categorical variables. Multiple logistic regression analysis was used to evaluate the impact of multivessel disease on impaired myocardial perfusion after adjustment for significant ($P < 0.05$) confounding baseline characteristics. The difference in event rates between groups during the follow-up period was assessed by the Kaplan–Meier method using the log-rank test. Cox regression analysis was used to evaluate the impact of multivessel disease on survival after adjustment for significant ($P < 0.05$) confounding baseline characteristics.

Results

The study population comprised 1494 patients with STEMI. Multivessel disease was observed in 870 patients (58.2%); 510 patients had 2-vessel disease and 360 patients with greater or more than 3-vessel disease. Demographic, clinical and angiographic characteristics according to the number of diseased vessels are reported in Table 1. The extent of CAD was associated with age, prevalence of diabetes, hypertension, previous myocardial infarction, previous revascularization, abciximab treatment and longer ischaemic time, and was inversely related to stent implantation, smoking and anterior myocardial infarction.

As shown on Fig. 1, the extent of CAD was linearly associated with impaired epicardial reperfusion (TIMI 0–2 flow) (odds ratio [OR], 1.49, 95% confidence interval [CI] 1.21–1.84, $P < 0.001$) and myocardial perfusion (grade 0–2) (OR 1.23, 95% CI 1.07–1.43, $P = 0.005$), even though no difference was observed in terms of complete ST-segment resolution and distal embolization. The impact of number of diseased vessels on impaired myocardial perfusion was confirmed after adjustment for confounding factors (age, diabetes, smoking, previous myocardial infarction, previous revascularization, anterior myocardial infarction, abciximab

Table 1 Patients' clinical and procedural characteristics according to Multivessel Disease.

Variable	I VD (n = 624)	II VD (n = 510)	III VD (n = 360)	P value (trend)
Clinical				
Age (years)	58.2 ± 12.1	61.6 ± 11.4	64.8 ± 11.9	< 0.001
Female gender (%)	23.2	22.0	23.1	0.88
Hypertension (%)	38.5	45.9	46.9	0.005
Diabetes (%)	13.5	18.6	22.8	< 0.001
Smoking (%)	56.3	53.5	43.3	< 0.001
Hypercholesterolemia (%)	36.2	36.9	38.1	0.57
Previous myocardial infarction (%)	3	10.0	17.2	< 0.001
Anterior myocardial infarction (%)	50.6	42.0	38.2	< 0.001
Previous revascularization (%)	4	7.8	14.7	< 0.001
Killip class > 1	9.6	14.4	12.7	0.12
Time-to-treatment (min)	221 ± 130	250 ± 169	272 ± 274	< 0.001
Angiographic				
Preprocedural TIMI 3 flow	19.8	17.4	16	0.12
Coronary stenting (%)	85.9	86.6	79.3	0.02
Abciximab (%)	40.1	32.7	26.4	< 0.001
Early GP IIb/IIIa inhibitors (%)	51.3	50.0	50.6	0.78
Postprocedural TIMI 3 flow (%)	86.9	87.8	96.2	< 0.001
Postprocedural myocardial blush grade 3 (%)	52.2	46.2	42	0.005
Distal embolization (%)	10.4	11.2	12.6	0.36
Complete ST resolution	56.4	57.9	58.1	0.6

VD: vessel disease; GP: glycoprotein; TIMI: thrombolysis in myocardial infarction.

administration, postprocedural TIMI 3 flow) (adjusted OR 1.18, 95% CI 1.01–1.40, $P=0.049$).

As shown on Fig. 2, at 208 ± 160 days of follow-up the extent of CAD was associated with higher mortality (HR 1.76, 95% CI 1.25–2.34, $P=0.002$), which was confirmed after correction for baseline confounding factors (age, diabetes, smoking, previous myocardial infarction, previous revascularization, anterior myocardial infarction, abciximab administration, postprocedural TIMI 3 flow and myocardial blush grade 3) (adjusted HR 1.54, 95% CI 1.06–2.24, $P=0.022$) (Table 2). As shown on Fig. 3, the presence of

multivessel disease did not affect the benefits from early administration of GP IIb/IIIa inhibitor therapy.

Discussion

The main finding from this study is that among STEMI patients undergoing primary angioplasty who received GP IIb/IIIa inhibitors treatment, multivessel disease is independently associated with impaired myocardial perfusion and mortality. Even though primary angioplasty has demon-

Table 2 Cox regression analysis for mortality.

Variable ^a	Hazard ratio	95% confidence interval	P value
Number of diseased vessels (per increase in number)	1.54	1.06, 2.24	0.022
Abciximab treatment	1.85	0.85, 2.25	0.19
Age > 75 years	7.45	3.67, 15.1	< 0.001
Smoking	1.75	0.75, 1.87	0.49
Diabetes	2.04	1.06, 3.94	0.033
Previous myocardial infarction	3.02	1.06, 8.63	0.039
Previous revascularization	0.65	0.16, 2.62	0.55
Infarct-related artery ^b	1.18	0.27, 5.14	0.82
Anterior myocardial infarction	2.94	1.44, 6.00	0.003
Myocardial blush grade 3	0.46	0.21, 0.98	0.043
Postprocedural TIMI 3 flow	0.45	0.20, 0.96	0.038

TIMI: thrombolysis in myocardial infarction.

^a All variables were entered in block in the model.

^b Left anterior descending vs non-left anterior descending.

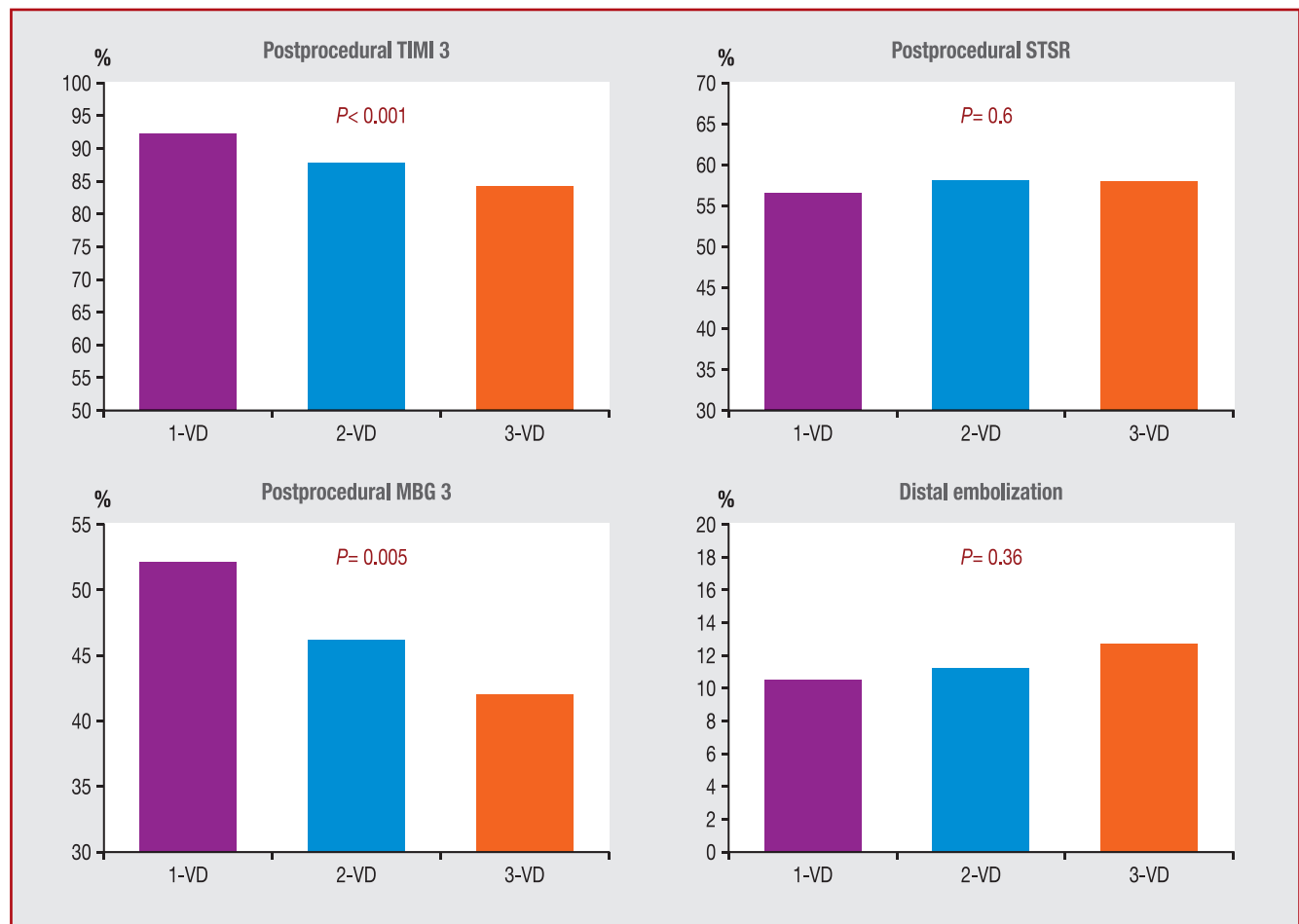


Figure 1. Impact of vessel disease on postprocedural TIMI 3 flow, complete ST-segment resolution (STSR), myocardial blush grade (MBG) 3 and distal embolization.

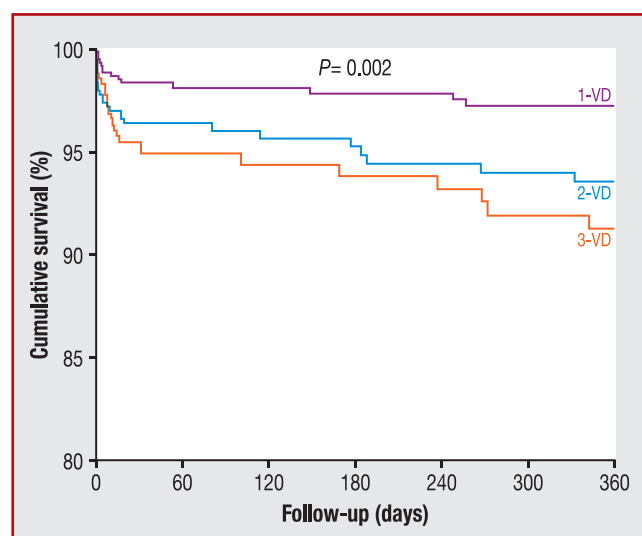


Figure 2. Kaplan–Meier survival curves showing significant impact of vessel disease on survival.

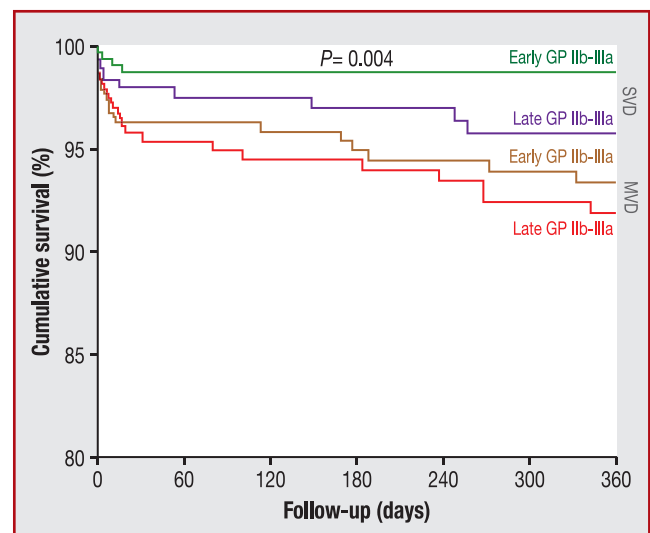


Figure 3. Kaplan–Meier survival curves showing the outcome of early and late administration of GP IIb/IIIa inhibitors according to vessel disease. MVD = multivessel disease; SVD = single vessel disease.

strated improved survival compared with thrombolysis in patients with STEMI, clinical outcome remains unsatisfactory in some subgroups. Multivessel disease is observed in approximately 50% of patients undergoing primary PCI and has been associated with poorer clinical outcomes [13–17]. However, few studies have examined the prognostic impact of the angiographic extent of CAD after primary PCI, especially in the contemporary era in which stents and glycoprotein IIb/IIIa inhibitors that have become standard of care [5].

In a report from the CADILLAC trial [23], Sorajja et al. reported that the presence of multivessel disease was a powerful independent predictor of mortality, even after adjustment for differences in baseline clinical and angiographic variables. Moreover, the negative prognostic impact of multivessel disease was not impacted by the use of stents or glycoprotein IIb/IIIa inhibitors. A significantly better outcome was observed among patients who received adjunctive revascularization of the non-IRA. In contrast to the CADILLAC study, in our investigation all patients received GP IIb/IIIa inhibitor treatment and most were treated with coronary stenting. Similarly to the CADILLAC experience, we observed that multivessel disease was independently associated with impaired myocardial perfusion and mortality. Several factors may in part explain the worse outcome observed in patients with multivessel disease. In accordance with previous studies, we found that patients with multivessel disease have a greater incidence of high-risk baseline features that may contribute to an adverse prognosis. Impaired myocardial reperfusion may additionally contribute to the worse outcome. Several hypotheses may help to explain this observation, and which certainly need further investigation. Multivessel CAD is a marker of more disseminated atherosclerosis, with microcirculatory involvement in the infarct vessel, which may directly diminish myocardial perfusion. Furthermore, it may reflect a large atherosclerotic burden in the IRA, which may determine a greater amount of distal embolization and subsequent capillary plugging [24]. Finally, multivessel disease may be a marker of endothelial dysfunction [25] or indicate greater systemic inflammation [26]. Recent studies have shown significant mortality benefits from the use of manual thrombectomy devices [9,10], which should therefore be strongly considered in these high-risk patients in order to improve reperfusion and survival. Despite its high prevalence, few data have been reported so far on the optimal management of patients with acute myocardial infarction and multivessel disease. Reports regarding the need for and timing of subsequent revascularization of diseased vessels following acute myocardial infarction have been limited to retrospective analyses of surgical series, and have not led to a clear consensus. A small randomized trial was stopped prematurely due to slow recruitment [27]. In a recent randomized trial [28], 214 consecutive patients with STEMI and multivessel CAD undergoing primary angioplasty were randomized before the first angioplasty to one of three strategies:

- culprit vessel angioplasty only;
- staged revascularization and;
- simultaneous treatment of non-IRAs.

During a mean follow-up of 2.5 years, 42 (50.0%) patients in the 'culprit vessel angioplasty only' group experienced

at least one major adverse cardiac event, 13 (20.0%) had an event in the staged revascularization group, and 15 (23.1%) in the simultaneous treatment of non-IRAs group ($P < 0.001$). In-hospital death, repeat revascularization and rehospitalization occurred more frequently in the culprit vessel angioplasty only group (all $P < 0.05$), while there was no significant difference in reinfarction among the three groups.

A recent meta-analysis of randomized and non-randomized trials showed safety and efficacy of a multivessel PCI approach compared with culprit vessel angioplasty only, with a significant reduction in the rate of revascularizations, but no benefit in terms of death and re-myocardial infarction [29]. However, current guidelines recommend revascularization of non-IRA stenoses only in the presence of haemodynamic or electrical instability. Future large randomized trials, especially in the era of new generation drug-eluting stents, are certainly needed to evaluate whether an aggressive approach to obtain in-hospital complete revascularization might impact on long-term survival among STEMI patients with multivessel disease.

Study limitations

The major limitation of the current study is the absence of a centralized core-lab, even though angiographic and ECG data were analysed with similar criteria across trials. Enzymatic infarct size was estimated by peak CK and CK-MB, whereas the use of scintigraphy techniques could potentially have improved the results. The availability of the GRACE score and data on ejection fraction would have improved the quality of our results. Unfortunately, these data were not collected. Finally, data on non-target vessel revascularization during hospitalization or at follow-up were not routinely collected.

Conclusions

This study showed that among STEMI patients undergoing primary angioplasty and on GP IIb/IIIa inhibitor treatment, multivessel disease is independently associated with impaired myocardial perfusion and survival. Thus all efforts should be attempted to use adjunctive mechanical devices or pharmacotherapies to improve perfusion and clinical outcome in these high-risk patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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